



VA



U.S. Department of Veterans Affairs

Veterans Health Administration

Northwest Mental Illness Research, Education, and Clinical Center (NW MIRECC)

MDMA-Assisted Psychotherapy for PTSD

Chris Stauffer, MD
VA Portland Health Care System

4/6/2022



Disclaimer

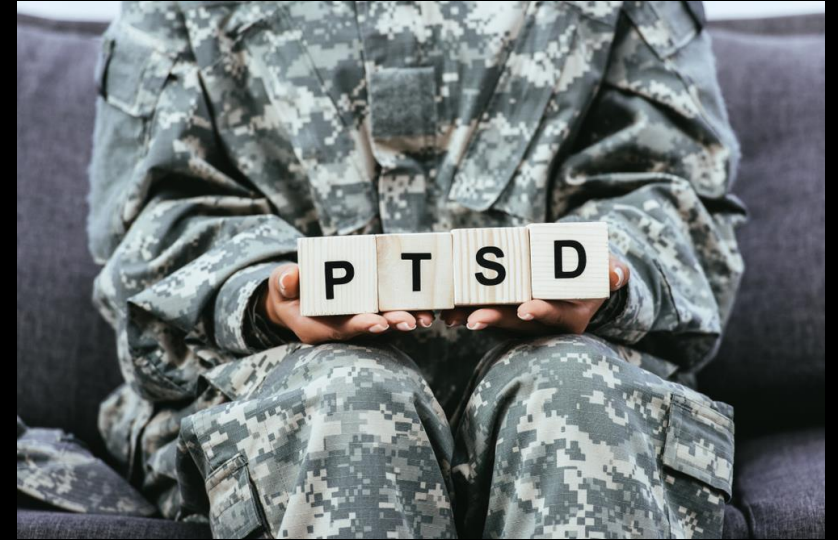
- MDMA is currently a Schedule I substance
 - The use of MDMA is restricted to clinical trial and expanded access settings

Course Learning Objectives

- Summarize MDMA-assisted psychotherapy for PTSD clinical trial outcomes
- Describe access and the pathway to FDA approval for MDMA-assisted psychotherapy
- Discuss current and upcoming VA studies of MDMA-assisted psychotherapy

PTSD

- 11-20% OIF/OEF Veterans have PTSD
- Third most prevalent service-connected disability
- >\$3 billion for PTSD care/year
- \$17 billion on service-connection for PTSD



PTSD: 2017 VA/DoD Clinical Practice Guidelines

PSYCHOTHERAPY



Cognitive Processing Therapy (CPT)

CPT teaches you how to change the upsetting thoughts and feelings you have had since your trauma.



Prolonged Exposure (PE)

PE teaches you to gradually approach trauma-related memories, feelings, and situations you have been avoiding since your trauma.

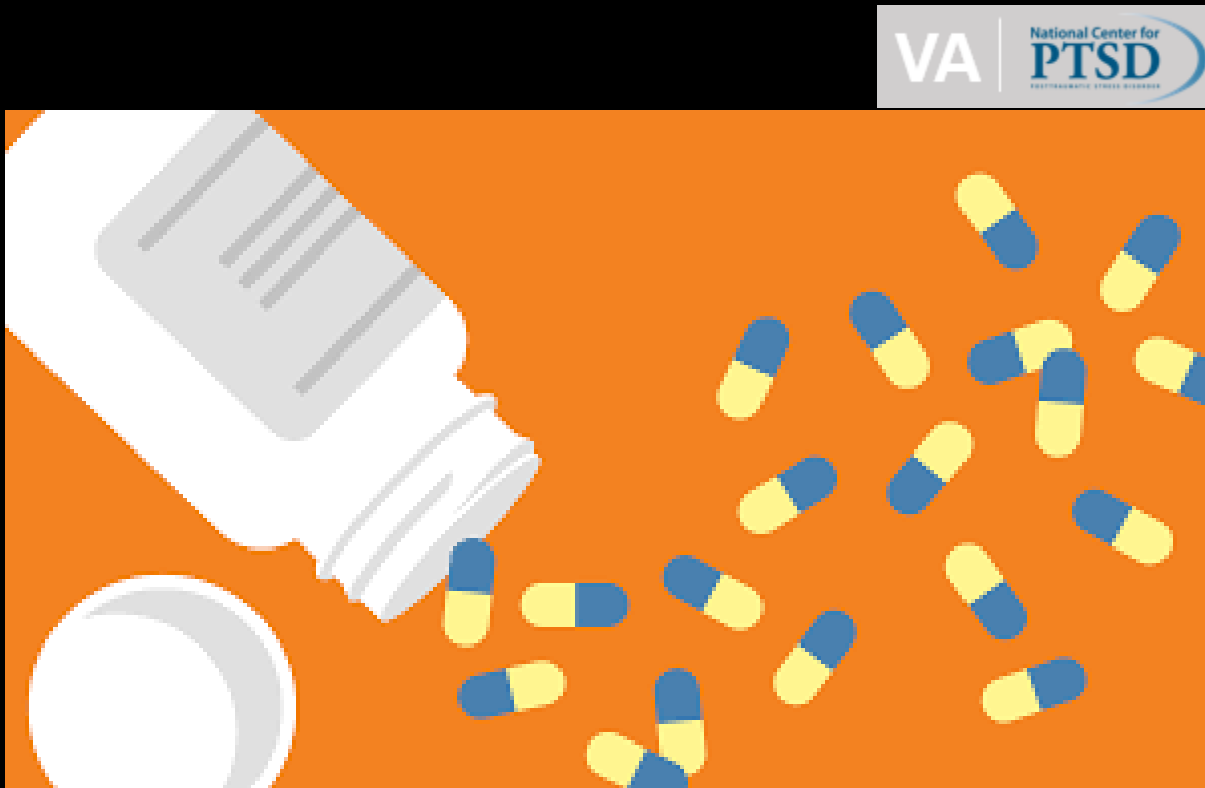


Eye Movement Desensitization and Reprocessing (EMDR)

EMDR helps you process and make sense of your trauma while paying attention to a back-and-forth movement or sound (such as a light or tone).

PTSD: 2017 VA/DoD Clinical Practice Guidelines

MEDICATIONS



- **Paroxetine**
- **Sertraline**
- **Fluoxetine**
- **Venlafaxine**

MDMA: Timeline in Medicine

- **1912**: Merck first synthesizes MDMA
- **1970's**: Psychoactive properties discovered, first legal use as adjunct to psychotherapy
- **1980's**: Recreational use increases
- **1985**: DEA designates MDMA as Schedule I substance



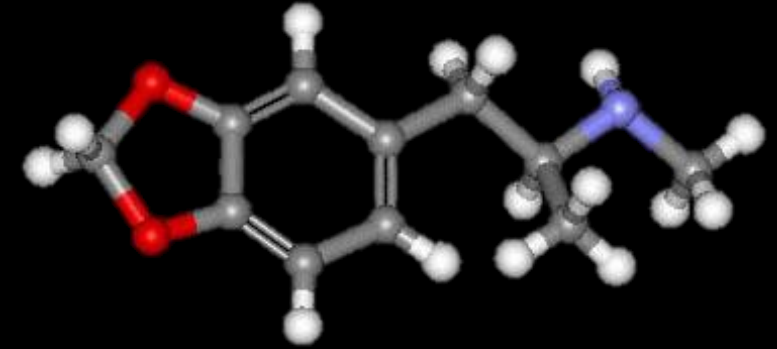
MDMA: Timeline in Medicine

- **1986**: Multidisciplinary Association of Psychedelic Studies (**MAPS**) is founded
- **1992**: First **Phase 1** human safety study
- **2004**: First **Phase 2** clinical trial of **MDMA-Assisted Psychotherapy for PTSD** begins enrollment
- **2017**: FDA designates **Breakthrough Therapy** status
- **2018**: First **Phase 3** clinical trial begins enrollment
- **2022**: **Expanded Access** begins enrollment at select sites

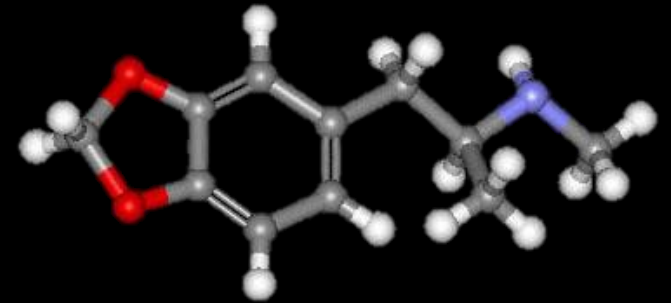
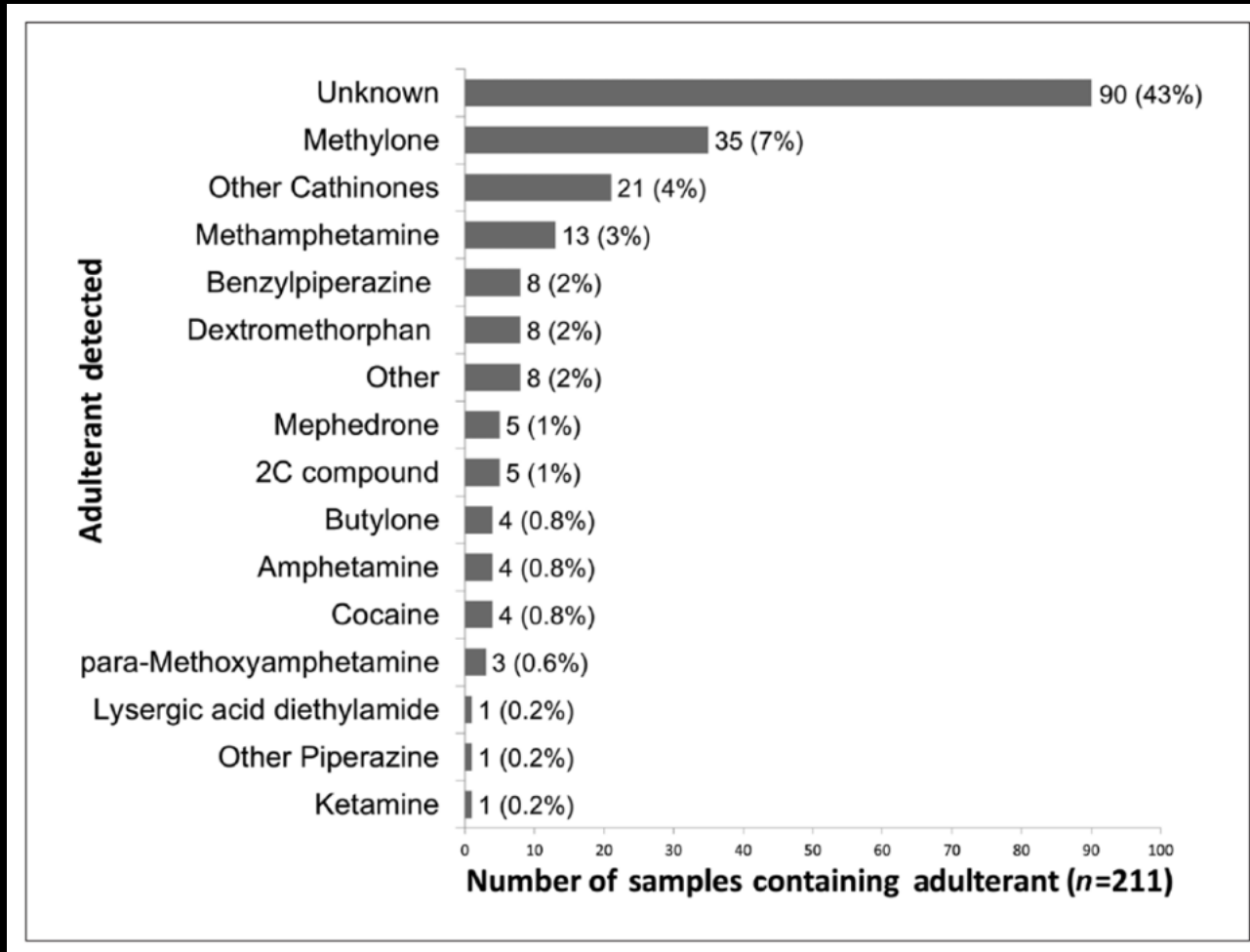


MDMA (\pm 3,4-methylenedioxymethamphetamine)

- Ring substituted phenethylamine
 - Chemically related to amphetamines
 - Unique pharmacologic properties
 - ↑ social engagement (Kirkpatrick & de Wit 2015)
 - ↑ openness (Wagner et al. 2017)
 - ↑ receptiveness to positive affect (Hysek et al. 2012)
 - ↑ empathy (Hysek et al. 2014)
 - ↑ disclosure of emotional content (Baggott et al. 2015)
 - “empathogen-entactogen”



Ecstasy: Morbidity & Mortality



≠



Ecstasy: Morbidity & Mortality



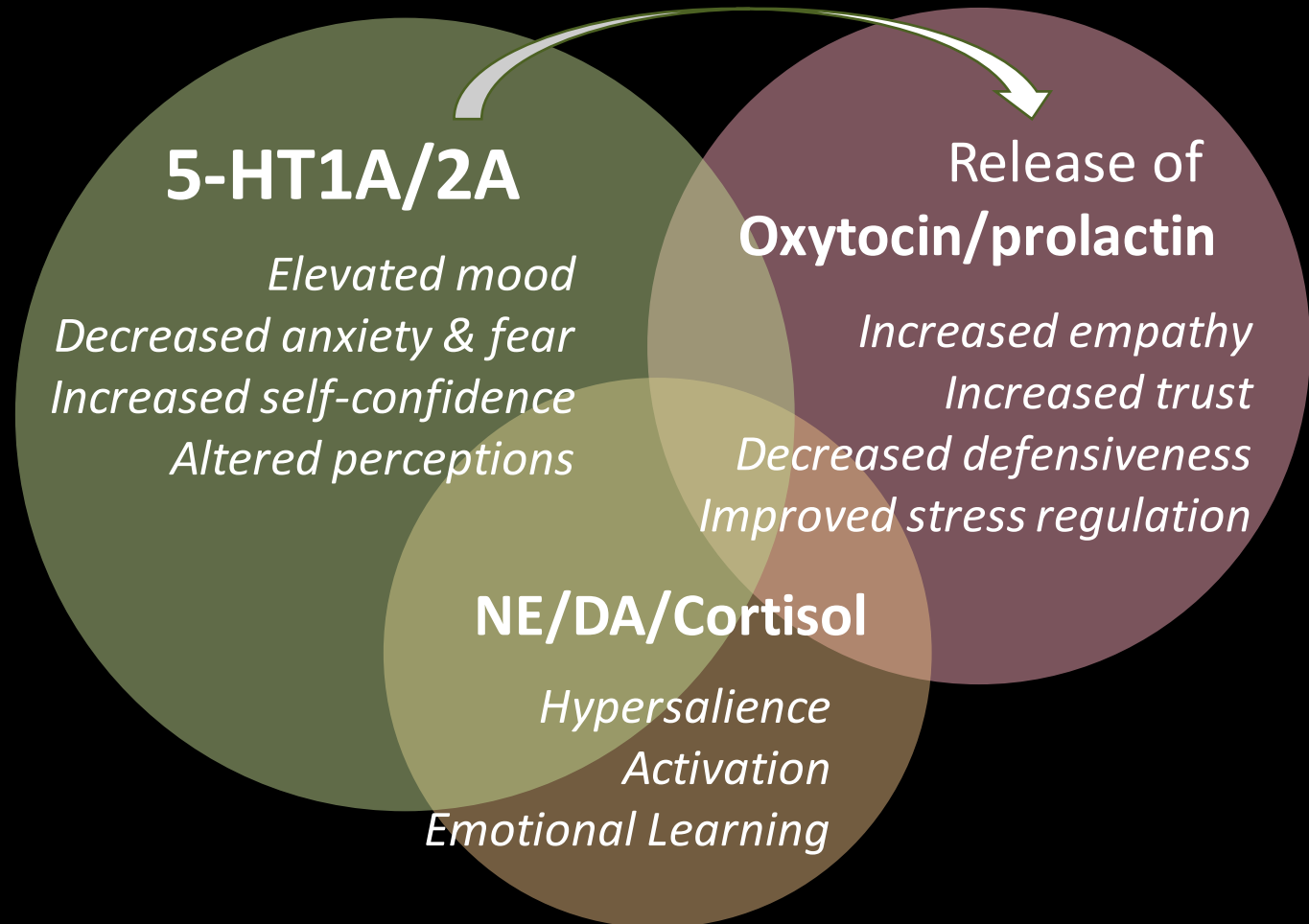
MDMA: Pharmacodynamics/Pharmacokinetics



- Dose 80-120mg + ½ dose @ 1.5-2hrs
- Onset 30-60 mins
- Peak 75-120 mins
- Duration 3-6 hours
- Metabolism:
 - 80% CYP2D6/CYP3A4
 - 20% renally excreted unchanged

MDMA: Pharmacodynamics/Pharmacokinetics

- Receptor agonism
 - 5-HT_{1A/2A/2B/2C}
 - α ₁/ α _{2A}/ β -adrenergic
 - D₁/D₂ (dopamine)
 - M₁/M₂ (muscarinic)
 - H₁ (histamine)
- ↑ intrasynaptic monoamines
 - 5HT>>>>>NE>>DA
- Downstream release
 - Oxytocin/Vasopressin
 - Prolactin
 - ACTH/cortisol



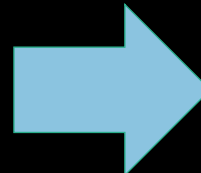
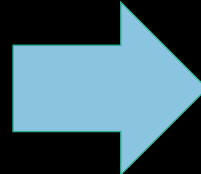
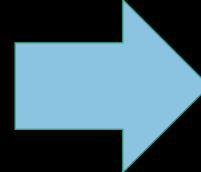
medication
assault stress
post traumatic stress disorder
neuroendocrinology
numbing
veterans
disorder
flashbacks
nightmares
thinking feeling
cognitive
fear
memories
avoidance
irritable
emotional
symptoms
thoughts
trauma
hypervigilance
anxiety
trigger
anxious
horror
avoid
guilt
medic
hypervigilance
anxiety
trigger
anxious
horror
avoid
guilt
medic

Increased amygdalar activity

Decreased vmPFC activity

Avoidance/emotional numbing

Lack of trust, hypervigilance



Reduction in amygdalar activity

Activation in vmPFC activity

Increased access to traumatic memories without flooding

Increased sense of safety and trust



MDMA/PTSD: Therapeutic Elements

- Result of *interaction* between:
 - the effects of the medicine (drug)
 - the mindsets of the participant and the therapists (set)
 - the therapeutic environment (setting)
 - social support



≠



MDMA/PTSD: Manualized Approach

A Manual for MDMA-Assisted Psychotherapy in the Treatment of Posttraumatic Stress Disorder

Michael C. Mithoefer, M.D.

Other contributors:

June Ruse, Psy.D

Annie Mithoefer, B.S.N.

Lisa Jerome, Ph.D.

Rick Doblin, Ph.D.

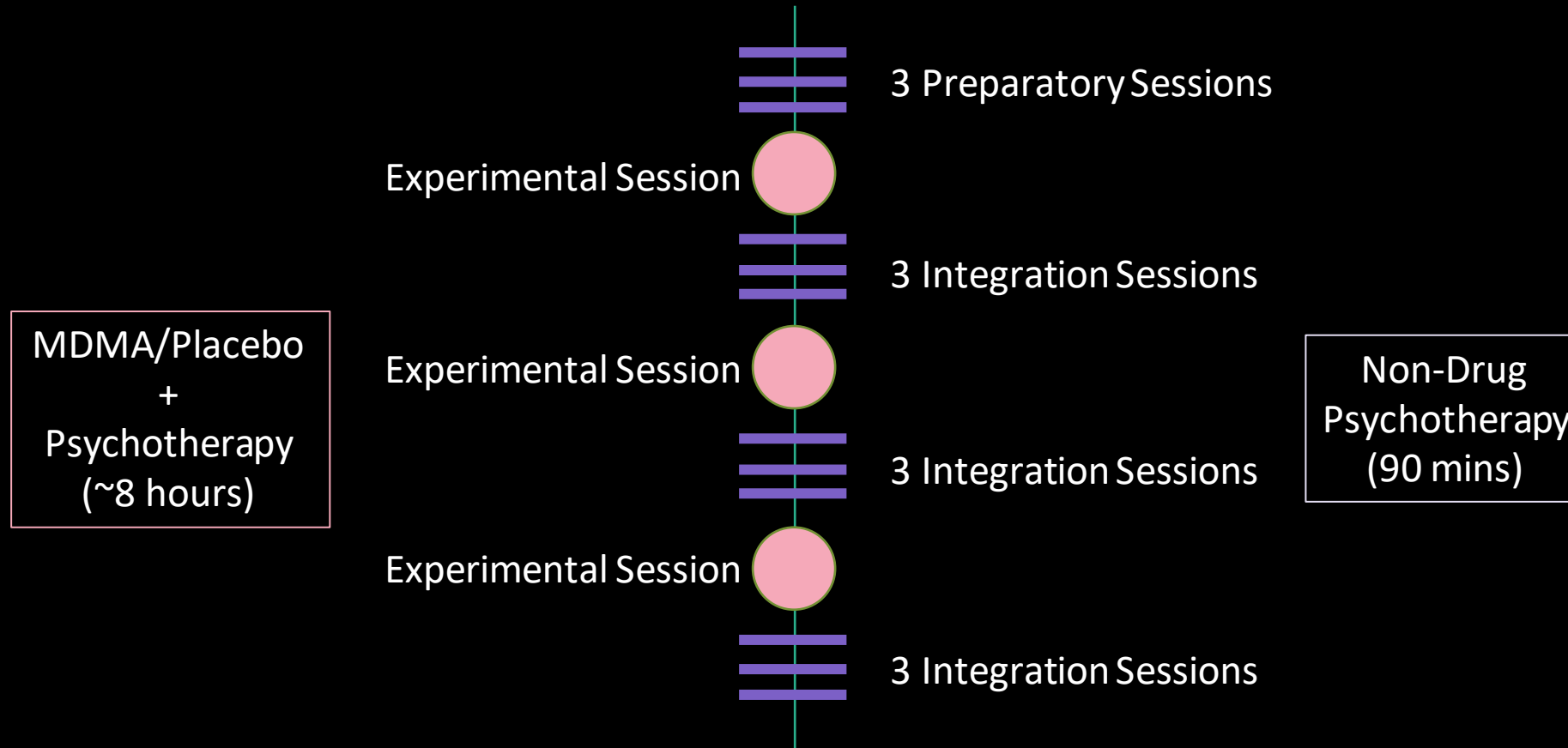
Elizabeth Gibson, M.S. Marcela

Ot'alora G., L.P.C.



<https://maps.org/2014/01/27/a-manual-for-mdma-assisted-therapy-in-the-treatment-of-ptsd/>

MDMA/PTSD: Clinical Trial Protocol



MDMA/PTSD: Potential Adverse Effects

- Physiological
 - Muscle tightness (63% v 11%)
 - Decreased appetite (52% v 11%)
 - Nausea (30% v 11%)
 - Increase in blood pressure and heart rate
- Psychological
 - Increased anxiety (70% v 55%)
- Interpersonal



MDMA/PTSD: Contraindications

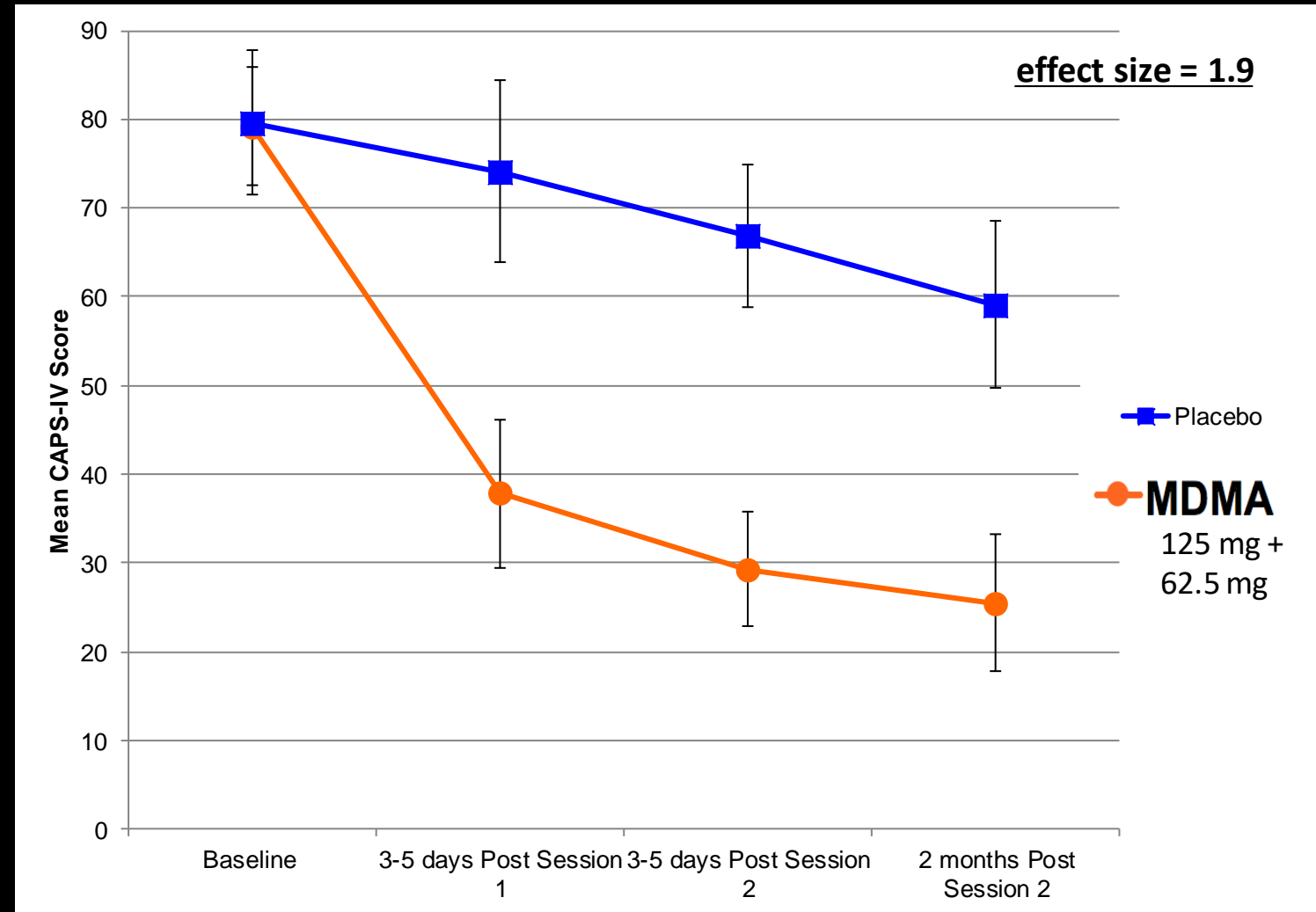
- Pre-existing cardiac or cerebrovascular disease
 - Exception is controlled hypertension with normal cardiac tests
- Primary psychotic disorder
- Bipolar I disorder
- Pregnancy
- Concomitant psychiatric medications



MDMA/PTSD: Phase 2 Trial

Chronic, Severe, Tx-Refractory PTSD (n=20)

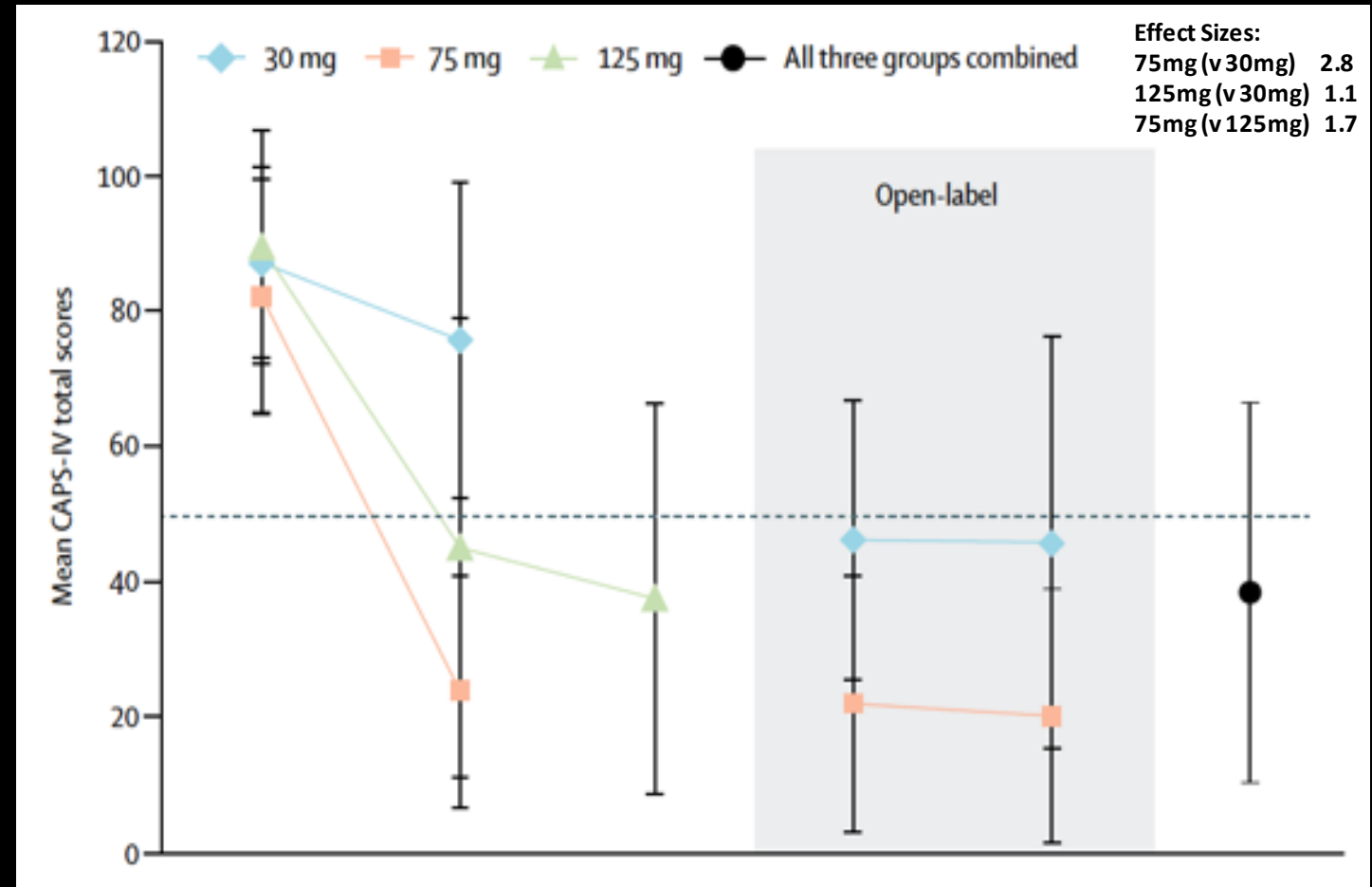
Characteristic	(n = 20)
Age, mean (SD)	40.4yrs (7.2)
Male	15%
Married	50%
PTSD, # years	20.67 (14.42)
Disability for PTSD	15%
Childhood Sexual Abuse	40%
Hx substance use d/o	15%
Comorbid MDD	80%
Comorbid anxiety d/o	15%
Therapy, # years	4.88 (4.13)
Med Trial	4.2
Baseline CAPS-IV	79.4 (22.4)



MDMA/PTSD: Phase 2 Trial

Veterans/First Responders (n=26)

Characteristic	(n=26)
Age, mean (SD)	37.2yrs (10.3)
Male	73%
Military Trauma (vs firefighters/police)	85%
PTSD, # years	7.12 (5.33)
Pre-Study Therapy	
CBT	92%
Prolonged Exposure	19%
Group Therapy	27%
Pre-Study Psychiatric Meds	
Antidepressants	96%
Anxiolytics	88%
Antipsychotics	38%
Sleep Aids	50%
Comorbid MDD	77%
Suicidal Ideation, history	85%
Suicidal Behavior, history	42%
Baseline CAPS-IV	86.5 (16.2)

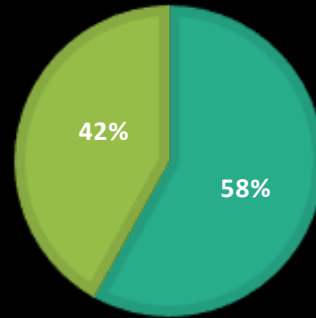


MDMA/PTSD: Phase 2 Trials (n=103)

**Control Group
(0-40 mg, n=31)**

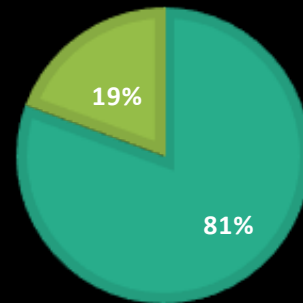
**SUBJECTS WITH 15 POINT
DROP IN CAPS-IV**

■ No ■ Yes

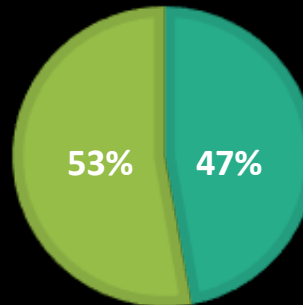
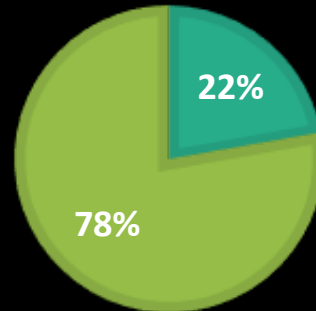


**SUBJECTS WITH 15 POINT
DROP & DID NOT MEET PTSD
CRITERIA**

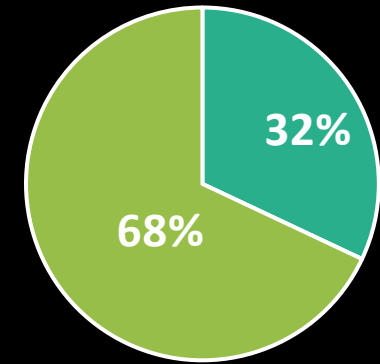
■ No ■ Yes



**Active MDMA Group
(75-125 mg, n=72)**



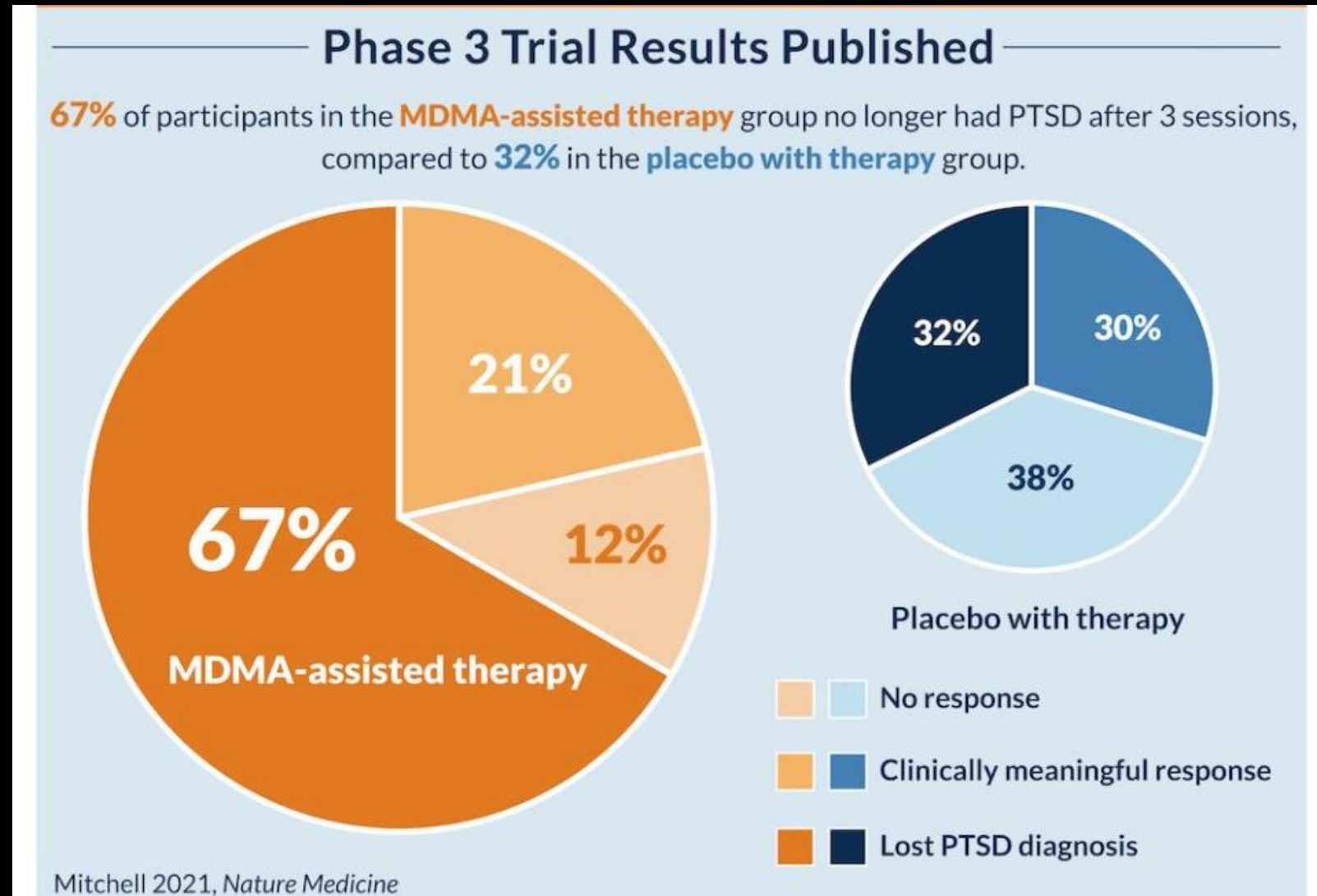
**SUBJECTS DID NOT MEET
PTSD CRITERIA AT 12-
MONTH FOLLOW-UP
(n=90)**



■ No ■ Yes

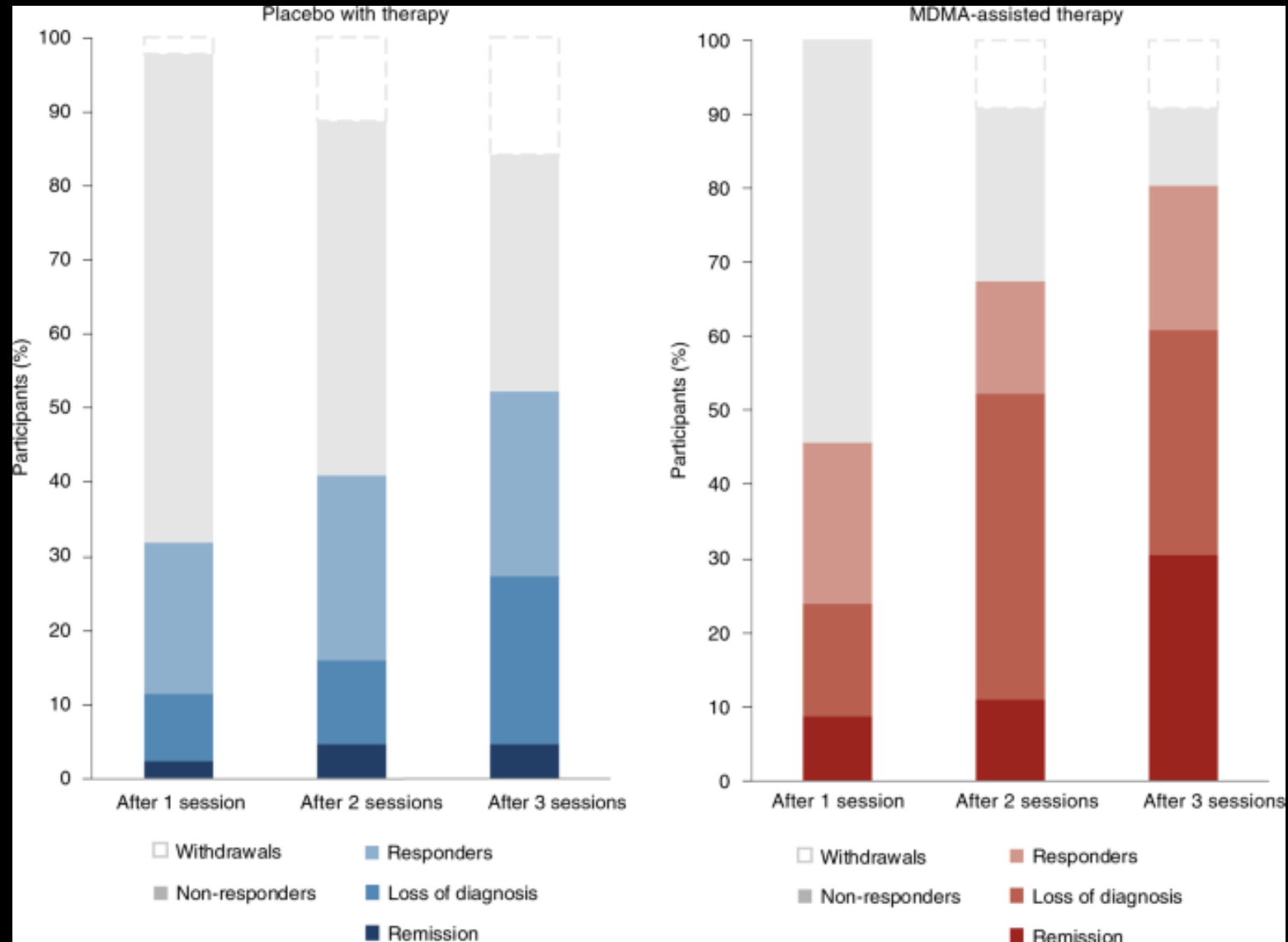
MDMA/PTSD: Phase 3 Trial (n=90)

Characteristic	(n = 90)
Age, mean (SD)	41 yrs (11.9)
Female	65.6%
PTSD, # years	14.1 yrs (11.5)
Dissociative subtype PTSD	21.1%
Veteran	17.8%
Comorbid MDD	91.1%
Previous Therapy	97.8%
Sertraline trial	18.9%
Paroxetine trial	6.7%
Baseline CAPS-V	44.1 (6.0)



MDMA/PTSD: Phase 3 Trial (n=90)

effect size = 0.91



MDMA/PTSD: What is required for FDA-Approval?

- Complete second **Phase 3** study October 2022
- Present **New Drug Application** to FDA
- **FDA-approval** by 2023?
- If so, first FDA-approved **medication-psychotherapy combination**
 - REMS Program
 - Prescriber training
 - Therapist training and supervision



MDMA/PTSD: Cost Effectiveness

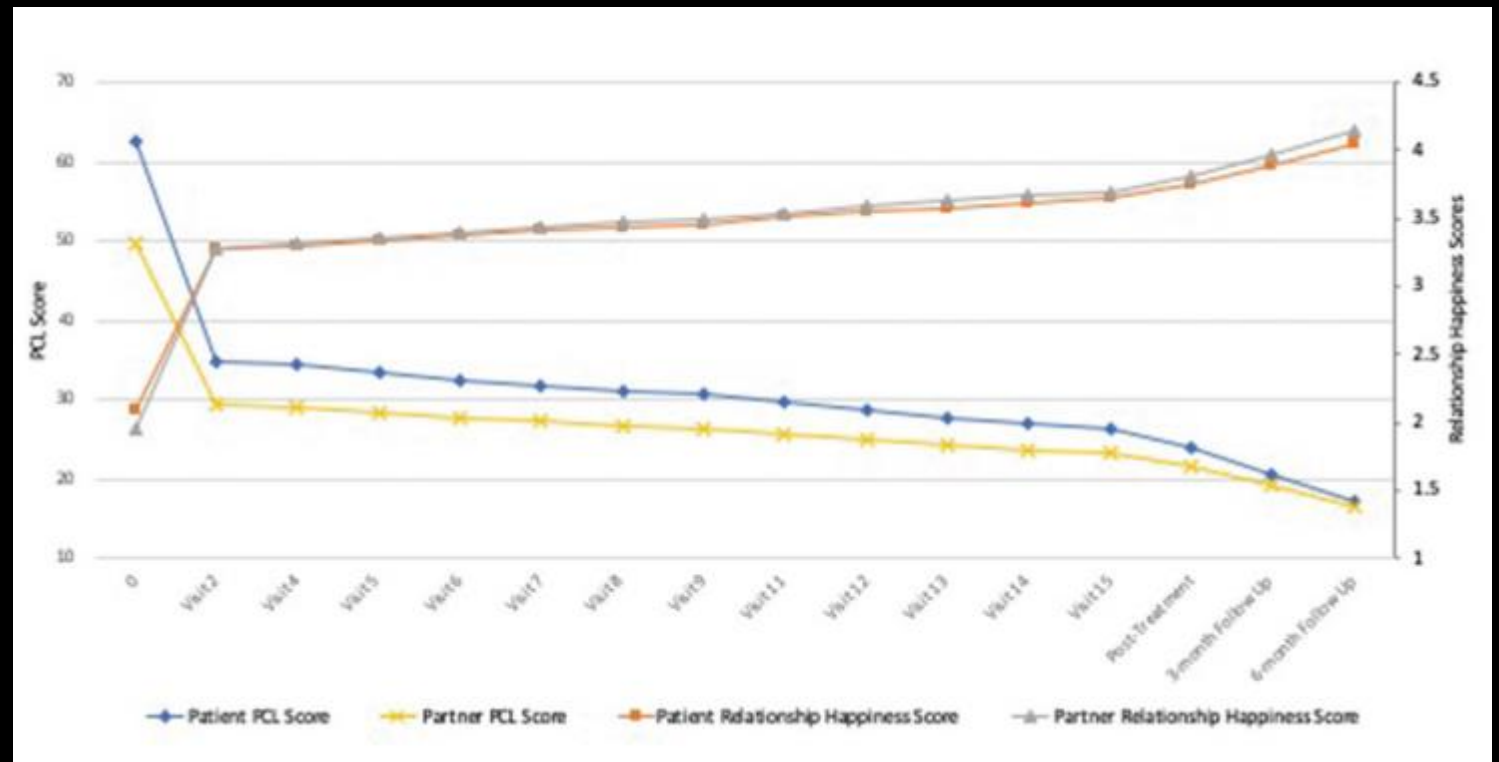
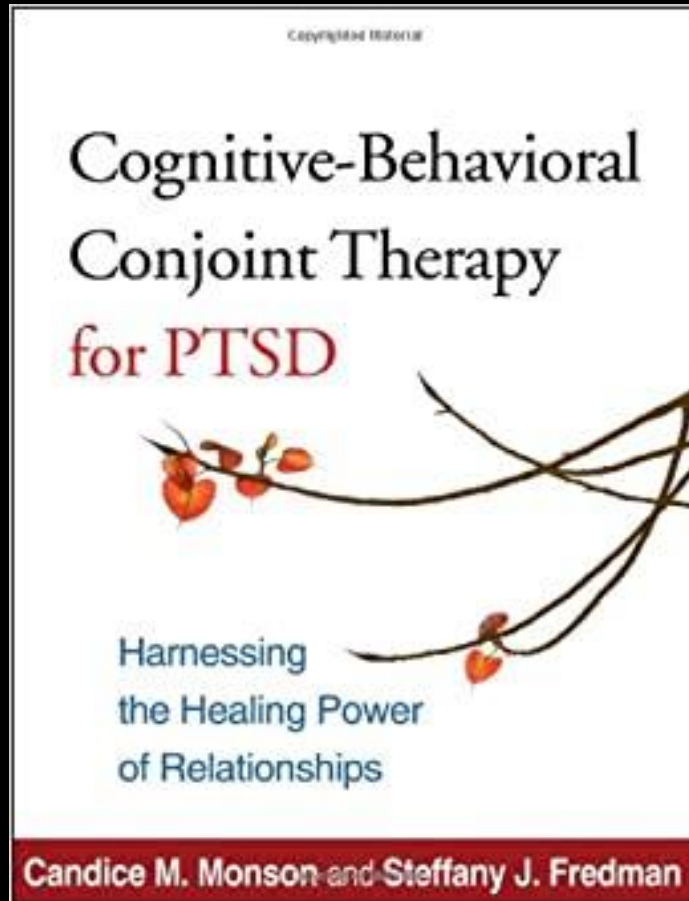
Phase 2: 2-3 prep + 2 MDMA + 6-8 integration

- \$7,543 per patient (91.2% therapists' compensation)
- For each 1,000 patients treated:
 - 30-yr saving to medical system = \$103 million, 5,553 QALYs, averts 42.9 deaths
- Breaks even at 3.1 years

Phase 3: 3 prep + 3 MDMA + 9 integration

- \$11,537 per patient
- For each 1,000 patients treated:
 - 30-yr saving to medical system = \$132.9 million, 4,856 QALYs, and averts 61.4 deaths
- Breaks even at 3.8 years

MDMA/PTSD: Cognitive-Behavioral Conjoint Couples Therapy (n=6 couples)



Marine Veteran

2 tours in Iraq
turret gunner on a humvee

First MDMA-assisted session

MDMA/PTSD: VHA Research

- **Loma Linda VA** (*PI: Shannon Remick*)



- **VA Portland Health Care System** (*PI: Chris Stauffer*)
 - MDMA-Assisted Group Therapy for PTSD



- **VA Greater Los Angeles Healthcare System** (*PI: Stephanie L. Taylor & Stephen Marder*)



- **Bronx VA/Icahn School of Medicine** (*PI: Rachel Yehuda*)



- 2 vs 3 MDMA sessions
 - Training program for VA providers
 - Email Junhong.chen@va.gov
- <https://icahn.mssm.edu/research/center-psychedelic-psychotherapy-trauma-research>

- **San Diego VAMC** (*PI: Leslie A. Moreland*)
 - MDMA-assisted couples therapy



Questions?